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SYNTHESIS AND SOME TRANSFORMATIONS OF 2-(3-AMINO-1-PHENYLPROPYL)FURAN

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A preparative method was developed for the synthesis of ethyl furfurylidenecyanoacetate. Its condensation with phenylmagnesium bromide gave ethyl α-cyano-β-(2-furyl)hydrocinnamate, the decarboxylation of which led to β-(2-furyl)hydrocinnamonitrile. Reduction of this nitrile with lithium aluminum hydride gave 2-(3-amino-1-phenylpropyl)furan. Some of its transformations were studied.

Keywords: 2-(3-amino-1-phenylpropyl)furan, ethyl furfurylidenecyanoacetate, ethyl α-cyano-β-(2-furyl)hydrocinnamate, reduction, decarbethoxylation.

In a continuation of our research [1, 2] by the reaction of ethyl furfurylidenecyanoacetate (**1**) with phenylmagnesium bromide we obtained ethyl α-cyano-β-(2-furyl)hydrocinnamate (**2**), in the molecule of which there are simultaneously phenyl and furyl radicals at the asymmetric carbon atom. Its decarbethoxylation led to β-(2-furyl)hydrocinnamonitrile (**3**), while reduction of the latter with lithium aluminum hydride in ether or tetrahydrofuran gave 2-(3-amino-1-phenylpropyl)furan (**4**). Condensation of the amine **4** with various aromatic aldehydes and ketones gave the corresponding azomethines, which were reduced by sodium borohydride without isolation to the secondary amines **5-13**. With the chlorides of various acids the amides **14-16** were obtained, and with succinic and phthalic anhydrides substituted succinimide **17** and phthalimide **18** were obtained.

EXPERIMENTAL

The IR spectra were recorded in vaseline oil on a Varian Mercury-300 instrument (300 MHz) in deuterochloroform and DMSO-d_6 with TMS as internal standard (Table 2). The characteristics of compounds **2-18** are given in Table 1.

Ethyl Furfurylidenecyanoacetate (1). A mixture of furfural (42 g, 0.43 mol), ethyl cyanoacetate (50 g, 0.44 mol), and ammonium acetate (3 g) was boiled in benzene (300 ml) until completely dehydrated (about 10 h). The next day the obtained crystals were filtered off, washed with water and then with benzene, dried at room temperature, and recrystallized from benzene or distilled. Yield 79.8 g (95%). The IR spectrum and bp (138-141°C/2 mm Hg) of the obtained compound were identical with published data [3].

Ethyl α-Cyano-β-(2-furyl)hydrocinnamate (2). A benzene solution of compound **1** (33.6 g, 0.18 mol) was added to an ether solution of the Grignard reagent obtained from magnesium (5.3 g, 0.22 mol) and bromobenzene (38 g, 0.22 mol) with gentle boiling and stirring. The reaction mixture was stirred at 42-44°C for

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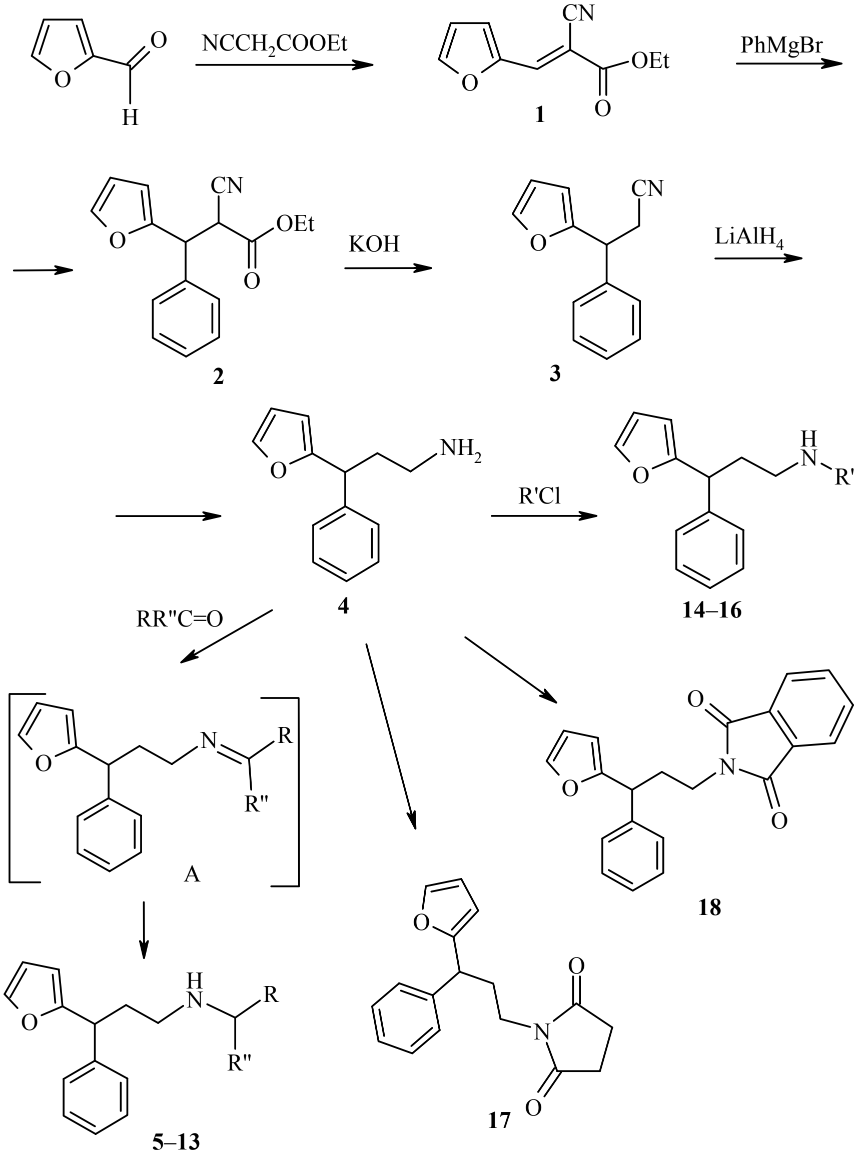

5–11 R'' = H; **5** R = MeOC$_6$H$_4$-*p*; **6** R = *i*-PrOC$_6$H$_4$-*p*; **7** R = 3,4-(CH$_3$O)$_2$C$_6$H$_3$; **8** R = *o*-FC$_6$H$_4$;
9 R = Ph; **10** R = *p*-Me$_2$NC$_6$H$_4$; **11** R = 2-furyl; **12** R = Ph, R'' = Me; **13** R = *p*-ClC$_6$H$_4$, R'' = Me;
14 R' = COCH$_2$CHMe$_2$; **15** R' = COCH$_2$Cl; **16** R' = *p*-SO$_2$C$_6$H$_4$Me

1.5 h. After cooling it was acidified with 10% hydrochloric acid, extracted with ether, washed with water, and dried, and after removal of the solvents it was distilled. We obtained 41 g (87%) of the product; bp 170°C/2 mm Hg. IR spectrum, ν, cm^{-1}: 1590, 1610 (C=C arom.), 1720 (CO), 2230 (CN).

β-(2-Furyl)hydrocinnamonitrile (3). Potassium hydroxide (14.6 g, 0.26 mol) was dissolved by heating in ethylene glycol (80 ml). The solution was added to the cyano ester **2** (35 g, 0.13 mol). The mixture was boiled with a reflux condenser for 3 h. The mixture was cooled, water (80 ml) was added, and product was extracted with ether, washed with water, and dried. After removal of the ether the product was distilled at reduced pressure. Yield 13.3 g (52%); bp 127°C/1 mm Hg. IR spectrum, ν, cm^{-1}: 1585, 1615 (C=C arom.), 2225 (CN).

2-(3-Amino-1-phenylpropyl)furan (4). To a cooled solution of lithium aluminum hydride (5.8 g, 0.15 mol) in dry ether (100 ml) we added dropwise an ether solution of the nitrile **3** (15 g, 0.076 mol), while keeping the temperature of the reaction mixture in the range of 0±2°C. The stirring was continued for a further

TABLE 1. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % Calculated, %			mp, °C bp, °C/mm	Yield, %
		C	H	N		
5	$C_{21}H_{23}NO_2$	78.53 78.47	7.16 7.21	4.40 4.35	210/2	92
6	$C_{23}H_{24}NO_2$	79.79 79.73	7.02 6.98	4.09 4.04	206-208	90
7	$C_{22}H_{26}NO_3$	75.07 75.01	7.50 7.44	4.00 3.97	208-210	87
8	$C_{20}H_{20}FNO$	77.60 77.64	6.45 6.51	4.56 4.51	185/1	93
9	$C_{20}H_{21}NO$	82.48 82.43	7.20 7.26	4.74 4.80	180/1	90
10	$C_{22}H_{24}N_2O$	79.53 79.48	7.33 7.27	8.36 8.42	205-208/1	83
11	$C_{18}H_{19}NO_2$	76.90 76.84	6.74 6.80	5.03 4.97	170/2	94
12	$C_{21}H_{23}NO$	82.63 82.58	7.53 7.59	4.54 4.58	178/1	76
13	$C_{21}H_{22}ClNO$	74.27 74.21	6.46 6.52	4.16 4.12	186-189/1	78
14	$C_{18}H_{23}NO_2$	75.81 75.75	8.18 8.12	5.00 4.90	185-187/1	87
15	$C_{15}H_{16}ClNO_2$	64.80 64.86	5.74 5.80	5.10 5.04	184-186/2	79
16	$C_{20}H_{21}NSO_3$	67.51 67.58	6.03 5.95	4.02 3.94	110-112	88
17	$C_{17}H_{17}NO_3$	70.10 70.02	6.06 6.00	5.02 4.94	195-197/1	63
18	$C_{21}H_{17}NO_3$	76.06 76.11	5.11 5.17	4.28 4.22	215-218/1	67

TABLE 2. The ^{1}H NMR Spectra for Compounds **2-4** ($CDCl_3$) and **5-18** (DMSO-d_6/CCl_4 1/3)

Compound	Chemical shifts, δ, ppm (SSCC, J, Hz)
1	2
2*	1.17 (3H, t, J = 7.1, CH_3); 4.16 (2H, q, J = 7.1, CH_2); 4.11 (0.5H, d, J = 7.5) and 4.33 (0.5H, d, J = 7.5, CHCN); 4.77 (0.5H, d, J = 7.5) and 4.82 (0.5H, d, J = 7.5, CHAr); 6.20 (0.5H, d, J = 3.3) and 6.34 (0.5H, dd, J_1 = 3.3, J_2 = 1.9, H_{fur}-4); 6.36 (1H, br. s, H_{fur}-3,4); 7.29-7.42 (5H, m, C_6H_5); 7.44 (0.5H, d, J = 1.9) and 7.46 (0.5H, d, J = 1.9, H_{fur}-5)
3	2.99 (1H, dd, J_1 = 14.6, J_2 = 7.7) and 3.13 (1H, dd, J_1 = 14.6, J_2 = 8.0, CH_2); 4.52 (1H, dd, J_1 = 7.7, J_2 = 8.0, CH); 6.11 (1H, d, J = 3.2, H_{fur}-3); 6.33 (1H, dd, J_1 = 3.3, J_2 = 1.8, H_{fur}-4); 7.26-7.40 (6H, m, H_{fur}-5, C_6H_5)
4	1.49 (2H, br. s, NH_2); 2.04 (1H, m) and 2.26 (1H, dq, J_1 = 13.3, J_2 = 7.2, CH_2); 2.67 (2H, m, NCH_2); 4.08 (1H, t, J = 7.7, CH); 6.08 (1H, d, J = 3.2, H_{fur}-3); 6.29 (1H, dd, J_1 = 3.2, J_2 = 1.8, H_{fur}-4); 7.19-7.34 (6H, m, H_{fur}-5, C_6H_5)
5	2.02 (1H, m) and 2.25 (1H, m, CH_2); 2.10 (1H, br, NH); 2.51 (2H, t, J = 6.6, NCH_2); 3.62 (2H, s, CH_2Ar); 3.77 (3H, s, OCH_3); 4.15 (1H, dd, J_1 = 8.1, J_2 = 7.7, CH); 6.06 (1H, d, J = 3.2, H_{fur}-3); 6.27 (1H, dd, J_1 = 3.2, J_2 = 2.0, H_{fur}-4); 6.79 (2H, m, H_{Ar}-3,5); 7.14-7.29 (7H, m, H_{Ar}-2,6, C_6H_5); 7.32 (1H, d, J = 2.0, H_{fur}-5)
6	1.31 (6H, d, J = 6.0, CH_3); 2.25 (1H, m) and 2.42 (1H, m, CH_2); 2.77 (2H, m, NCH_2); 3.99 (2H, s, CH_2Ar); 4.10 (1H, t, J = 7.7, CH); 4.57 (1H, q, J = 6.0, CH); 6.14 (1H, d, J = 3.2, H_{fur}-3); 6.28 (1H, dd, J_1 = 3.2, J_2 = 2.0, H_{fur}-4); 6.82 (2H, m, H_{Ar}-3,5); 7.15-7.37 (8H, m, H_{Ar}-2,6, C_6H_5, H_{fur}-5)
7	2.25 (1H, m) and 2.42 (1H, m, CH_2); 2.77 (2H, m, NCH_2); 3.77 (3H, s, OCH_3); 3.78 (3H, s, OCH_3); 3.96 (2H, s, CH_2Ar); 4.10 (1H, t, J = 7.7, CH); 6.14 (1H, d, J = 3.2, H_{fur}-3); 6.28 (1H, dd, J_1 = 3.2, J_2 = 2.0, H_{fur}-4); 6.81 (1H, d, J = 8.1, H_{Ar}-5); 6.89 (1H, dd, J_1 = 8.1, J_2 = 2.0, H_{Ar}-6); 7.12 (1H, d, J = 8.0, H_{Ar}-2); 7.15-7.29 (5H, m, C_6H_5)

TABLE 2 (continued)

1	2
8	1.77 (1H, br, NH); 2.05 (1H, m) and 2.28 (1H, dq, J_1 = 13.8, J_2 = 6.9, CH_2); 2.54 (2H, m, NCH_2); 3.76 (2H, s, CH_2Ar); 4.18 (1H, t, J = 7.7, CH); 6.08 (1H, d, J = 3.2, H_{fur}-3); 6.28 (1H, dd, J_1 = 3.2, J_2 = 1.9, H_{fur}-4); 6.98-7.41 (10H, m, H_{fur}-5, C_6H_5, C_6H_4)
9	1.81 (1H, br, NH); 2.09 (1H, m) and 2.31 (1H, dq, J_1 = 13.8, J_2 = 6.9, CH_2); 2.58 (2H, m, NCH_2); 3.74 (2H, s, CH_2Ar); 4.21 (1H, t, J = 7.7, CH); 6.10 (1H, d, J = 3.2, H_{fur}-3); 6.31 (1H, dd, J_1 = 3.2, J_2 = 1.9, H_{fur}-4); 7.18-7.34 (10H, m, C_6H_5); 7.36 (1H, d, J = 1.9, H_{fur}-5)
10	1.68 (1H, br, NH); 2.03 (1H, m) and 2.26 (1H, dq, J_1 = 13.5, J_2 = 7.0, CH_2); 2.53 (2H, m, NCH_2); 2.93 (6H, s, $N(CH_3)_2$); 3.58 (1H, d, J = 13.0) and 3.60 (1H, d, J = 13.0, CH_2Ar); 4.16 (1H, t, J = 7.7, CH); 6.07 (1H, d, J = 3.2, H_{fur}-3); 6.28 (1H, dd, J_1 = 3.2, J_2 = 1.9, H_{fur}-4); 6.64 (2H, m, H_{Ar}-3,5); 7.10 (2H, m, H_{Ar}-2,6); 7.15-7.30 (5H, m, C_6H_5); 7.34 (1H, d, J = 1.9, H_{fur}-5)
11	1.70 (1H, br, NH); 2.01 (1H, dtd, J_1 = 13.5, J_2 = 8.3, J_3 = 6.6) and 2.24 (1H, dq, J_1 = 13.5, J_2 = 7.1, CH_2); 2.52 (2H, m, NCH_2); 3.68 (2H, s, CH_2Ar); 4.15 (1H, dd, J_1 = 8.3, J_2 = 7.1, CH); 6.07 (1H, d, J = 3.2, H_{fur}-3); 6.10 (1H, d, J = 3.2, H_{fur}-3); 6.28 (2H, dd, J_1 = 3.2, J_2 = 1.9, two H_{fur}-4); 7.15-7.30 (5H, m, C_6H_5); 7.33 (1H, d, J = 1.9, H_{fur}-5); 7.35 (1H, d, J = 1.9, H_{fur}-5)
12*	1.28 (3H, d, J = 6.6, CH_3); 1.47 (1H, br, NH); 1.91-2.44 (4H, m, CH_2, NCH_2); 3.64 (0.5H, q, J = 6.6) and 3.65 (0.5H, q, J = 6.6, NCH); 4.10 (0.5H, dd, J_1 = 8.6, J_2 = 6.7) and 4.14 (0.5H, t, J = 7.6, CH); 6.01 (0.5H, d, J = 3.3) and 6.03 (0.5H, d, J = 3.3, H_{fur}-3); 6.24 (0.5H, dd, J_1 = 3.2, J_2 = 2.0); 6.25 (0.5H, dd, J_1 = 3.2, J_2 = 2.0, H_{fur}-4); 7.14-7.26 (10H, m, two C_6H_5); 7.30 (0.5H, d, J = 2.0) and 7.31 (0.5H, d, J = 2.0, H_{fur}-5)
13*	1.25 (3H, d, J = 6.6, CH_3); 1.80 (1H, br, NH); 1.90-2.42 (4H, m, CH_2, NCH_2); 3.63 (0.5H, q, J = 6.6) and 3.64 (0.5H, q, J = 6.6, NCH); 4.08 (0.5H, dd, J_1 = 8.6, J_2 = 5.9) and 4.12 (0.5H, t, J = 7.6, CH); 6.01 (1H, d, J = 3.3, H_{fur}-3); 6.24 (1H, br. s, H_{fur}-4); 7.13-7.30 (10H, m, C_6H_4, C_6H_5, H_{fur}-5)
14	0.92 (6H, d, J = 6.5, CH_3); 1.92 (2H, d, J = 6.8, $C(O)CH_2$); 1.95-2.07 (4H, m, CH_2, NCH_2); 2.22 (1H, m, CH); 3.01 (2H, m, NCH_2); 4.01 (1H, t, J = 7.6, CH), 6.11 (1H, d, J = 3.2, H_{fur}-3); 6.27 (1H, dd, J_1 = 3.2, J_2 = 1.9, H_{fur}-4); 7.14-7.29 (5H, m, C_6H_5); 7.33 (1H, d, J = 1.9, H_{fur}-5); 7.47 (1H, br. t, J = 5.7, NH)
15	2.06 (1H, dq, J_1 = 13.6, J_2 = 7.0) and 2.28 (1H, dq, J_1 = 13.6, J_2 = 7.2, CH_2); 3.11 (2H, m, NCH_2); 3.90 (2H, s, CH_2Cl); 4.03 (1H, t, J = 7.6, CH); 6.13 (1H, d, J = 3.3, H_{fur}-3); 6.28 (1H, dd, J_1 = 3.3, J_2 = 2.0, H_{fur}-4); 7.15-7.30 (5H, m, C_6H_5); 7.34 (1H, d, J = 2.0, H_{fur}-5); 7.95 (1H, br. t, J = 5.5, NH)
16	1.94 (1H, dtd, J_1 = 13.6, J_2 = 7.7, J_3 = 6.5) and 2.18 (1H, dtd, J_1 = 13.6, J_2 = 7.7, J_3 = 6.5, CH_2); 2.42 (3H, s, CH_3); 2.67 (2H, td, J_1 = 6.5, J_2 = 5.8, NCH_2); 4.04 (1H, t, J = 7.7, CH); 6.02 (1H, d, J = 3.2, H_{fur}-3); 6.24 (1H, dd, J_1 = 3.2, J_2 = 1.9, H_{fur}-4); 7.12-7.28 (7H, m, C_6H_5, H_{Ar}-3,5); 7.30 (1H, d, J = 1.9, H_{fur}-5); 7.41 (1H, br. t, J = 5.8, NH); 7.62 (2H, m, H_{Ar}-2,6)
17	2.19 (1H, dtd, J_1 = 13.9, J_2 = 7.6, J_3 = 6.5) and 2.34 (1H, dtd, J_1 = 13.6, J_2 = 7.6, J_3 = 6.5, CH_2); 2.49 (4H, s, $(CH_2)_2$); 3.46 (2H, m, NCH_2); 4.02 (1H, t, J = 7.6, CH); 6.12 (1H, d, J = 3.1, H_{fur}-3); 6.30 (1H, dd, J_1 = 3.1, J_2 = 1.9, H_{fur}-4); 7.18-7.33 (5H, m, C_6H_5); 7.36 (1H, d, J = 1.9, H_{fur}-5)
18	2.26 (1H, dtd, J_1 = 14.3, J_2 = 8.1, J_3 = 6.6) and 2.42 (1H, dtd, J_1 = 14.3, J_2 = 7.5, J_3 = 6.6, CH_2); 3.62 (2H, m, NCH_2); 4.05 (1H, dd, J_1 = 8.1, J_2 = 7.5, CH); 6.10 (1H, d, J = 3.2, H_{fur}-3); 6.23 (1H, dd, J_1 = 3.2, J_2 = 1.9, H_{fur}-4); 7.13 (1H, m) and 7.22-7.25 (4H, m, C_6H_5); 7.30 (1H, d, J = 1.9, H_{fur}-5); 7.72-7.80 (4H, m, C_6H_4)

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* A mixture of two diastereomers (~1:1).

hour at this temperature, the mixture was cooled to -10°C in a bath of ice and salt, and water (6 ml), 15% sodium hydroxide solution (6 ml), and water (17 ml) were added successively drop by drop. The inorganic precipitate was filtered off and washed with ether, combined organic extracts dried and after evaporation of the solvent the residue was distilled. We obtained 13 g (85%) of the amine **4**; bp 108°C/1 mm Hg. IR spectrum, ν, cm^{-1}: 1600, 1610 (C=C arom.), 3300 (NH_2).

Synthesis of Compounds 5-13. A mixture of equimolar amounts of one of the aromatic aldehydes (or ketones, in the case of aromatic ketones xylene was used as solvent) and the amine **4** in benzene was heated for 4 h with a Dean–Stark tube until completely dehydrated. The benzene was removed, the remaining mass was dissolved in methanol (0.1 mol of the azomethine and 40 ml of methanol), and an equimolar amount of sodium borohydride was added in portions with stirring and cooling with water so that the temperature of the reaction mixture did not exceed 20°C. The reaction mixture was then stirred for a further 1 h at room temperature. After distillation of the methanol the mixture was made alkaline with a 20% sodium hydroxide solution and extracted with ether. The extract was dried, the ether was distilled, and the remaining mass was distilled. The yields and constants of the obtained amines **5-13** are given in Table 1.

Synthesis of Amides 14-16. To a solution of the amine **4** (6 g, 0.03 mol) in absolute benzene (30 ml) and triethylamine (3 g, 0.032 mol) we added an equimolar amount of the respective acid chloride. The mixture was boiled with a reflux condenser for 4 h. After cooling the product was washed with water, extracted with benzene, and dried, and after distillation of the benzene the residue was distilled. Compounds **14-16** were obtained (Table 1).

N-[γ-Phenyl-γ-(2-furyl)propyl]succinimide (17) and the Phthalimide 18. A mixture of equimolar amounts of succinic (phthalic) anhydride and the amine **4** in benzene was heated for 10 h with a Dean–Stark tube until completely dehydrated. The benzene was distilled, and the remaining mass was distilled under vacuum (Table 1).

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